The Examiner contends that the priority data is incorrect. Applicants have amended the first page of the application to recite the appropriate priority information. As amended the specification recites: This application is a continuation-in-part of application 08/436,265 which is a 371 of application serial no. PCT/GB93/02367 filed November 17, 1993.

Claim 21-24 and 26 stand rejected under 35 U.S.C. § 112, first paragraph for purportedly being non-enabled. In particular the Examiner contends that the claims encompass a molecule or agent that binds to ALK-1 wherein the binding phosphorylates Smad 1 and wherein the phosphorylation of Smad 1 enhances expression of a gene. The Examiner contends that there is nothing in the specification that the interaction of TGF-β and ALK-1 and the phosphorylation of Smad 1 enhances or inhibits gene expression (Office Action page 4). Claims 21-24 and 26 have been cancelled and thus the rejection as it applies to these claims is moot. Nonetheless applicants address the Examiner's comments.

A Patent need not teach and preferably omits, what is well known in the art.

Hybritech Inc. v. Monoclonal Antibodies, Inc. 231 USPQ 81, 94 (Fed. Cir. 1986)

It is well known to those of skill in the art at the time of filing this application that phosphorylated Smad 1 translocates to the nucleus and exerts transcriptional control on the genes therein. Those of skill in the art appreciated that the Smads were involved in signal transduction pathways downstream of serine/theonine kinase receptors (see Massague et al., *Trends Cell Biol.* 2:187-192 (1997) cited in the specification page 34, line 11-12), . A quick review on the internet reveals numerous articles on the effects of Smad 1 phosphorylation on cellular transcription; and see also Liu et al., *Nature,* 381:620-623 (1996), and Kretzschmer et al., *Genes Dev.* 11:984-995 (1997) who disclose that human Smad 1 has ventralizing activity (also cited in the specification page 34, lines 15-19) . As such, it is unnecessary to exemplify the effect of phosphorylated Smad 1 on cellular transcription to demonstrate that phosphorylated Smad 1 enhances gene expression.

Applicants have demonstrated that TGF-β binds and activates ALK-1 which in turn activates phosphorylation of Smad 1, see page 35, line 20 to page 36, line 7. The effects of phosphorylated Smad 1 are well known in the art. The Examiner has not presented any objective

support for why one of skill in the art would doubt that Smad 1 phosphorylated in response to an activated ALK-1 would not regulate transcription. As such, the claims are fully enabled by the specification and applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claims 21, 22, 26 and 28 stand rejected under 37 C.F.R. § 112, first paragraph for purportedly lacking adequate enablement for "molecule" or "agent" that binds to ALK-1. The Examiner states that the specification is enabling for TGF-β but that there are no other molecules described that bind to the extracellular domain of ALK-1 leading to phosphorylation of Smad 1 and enhance gene expression. The cancellation of claims 21, 22, 26 and 28 renders this rejection moot. The new claims 20, 30 and 31 which recite a TGF-β or portion of TGF-β that binds to ALK-1 are fully enabled by the specification.

The specification demonstrates that TGF-β activates ALK-1, on ALK-1 containing cells, and that ALK-1 activates phosphorylation of Smad-1. Those of skill in the art appreciate that phosphorylated Smad 1 regulates transcription. The claims require that cells express ALK-1 and that the cells be contacted with the TGF-β or a portion of TGF-β that is sufficient to bind ALK-1 and that the activated ALK-1 activates phosphorylation of Smad 1. As such the claims are fully enabled by the specification.

The Examiner further contends that the limitation to a "molecule" or "agent" in claims 21, 22, 26 and 28 is equivalent to a "single means" claim wherein the claim covers every conceivable structure for achieving the desired result while the specification discloses only those known to the inventor. In view of the cancellation of claim 21, 22, 26 and 28 rejection as it relates to these claims is moot. Claims 29, 30 and 31 do not recite the limitation of a "molecule" or an "agent."

In view of the foregoing remarks and amendments tot the claims applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims.

Claims 21, 22, 26 and 28 stand rejected under 35 U.S.C. § 112, first paragraph for purportedly lacking written description. In particular, the Examiner contends that the description of TGF-β alone is insufficient to describe the genus of molecules or agents that bind to ALK-1.

The Examiner contends that the specification does not place any limits on the structure of the molecule or agent or what distinguishing attributes the molecules or agents share. The cancellation of claims 21, 22, 26 and 28 renders this rejection moot.

The pending method claims relate to the activation of ALK-1, by TGF-β or a sufficient portion of TGF-β to bind AlK-1, and the subsequent phosphorylation of Smad 1. The claims also relate to the enhancing expression of a gene which is activated by phosphorylated Smad-1 or to the identification of genes having enhanced transcription in response to phosphorylated Smad 1 by contacting cells with TGF-β or a sufficient portion of TGF-β to bind AlK-1. Support for these claims is found, e.g., in claims 21, 23, 24 and 28 as initially filed.

In view of the foregoing amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

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